Review

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Analysis of Potential Confounding Variables in Epidemiologic Studies of Parental/Household Smoking and Respiratory Health in Preschool Children

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Abstract
In this analytical study, aspects of the design of 41 epidemiologic studies pertaining to the relationship between parental/household smoking and the prevalence of respiratory symptoms and certain illnesses in preschool children (0–5 years old) were examined using a systematic protocol developed previously for a similar analysis of epidemiologic studies in school-age or older children. Wide variability was observed from study to study in the consideration of 21 predetermined potential confounding variables. While the socioeconomic status (SES), family health history, subject's personal health history, family size, age and gender were considered in 50% or more of the studies, indoor pollution (other than gas stove usage), day care use, animal exposures, stress, dampness/cold, season, occupational exposures, nutritional status of the subject, and maternal smoking during pregnancy were considered infrequently (in <25% of the studies) or not at all. A wide variation was also observed from study to study in the array of confounders considered. When evaluated on the basis of number of confounders considered per study, only 3 of the 41 papers considered 10 or more of the 21 predetermined variables. The clinical endpoints, usually obtained from parental questionnaire responses, were validated by medical records or physician examination in only slightly more than 50% (21/41) of the relevant epidemiologic studies. Twelve of the 21 predetermined confounders were analyzed in detail. There was wide variation in and a lack of standardization of the criteria used as indices of SES, family and personal health history, and age. There was also marked variation among the studies in methods used, if any, to adjust for confounding variables. Several of the confounding variables that we looked at appeared to be consistently associated with increased risk of respiratory illness in preschool children, including family and personal health history, young age, male gender, day care use and season. On the other hand, no consistent association was observed for SES, artificial feeding, gas fuel use and indoor pollution, while equivocal or uncertain data in this regard were obtained for dampness/cold and heating/air-conditioning. While no consistent interactions between various confounders were observed, the relationship between parental/household smoking and respiratory illness in preschool children appeared to vary inversely related to age. Before epidemiologic associations between parental smoking and respiratory health in preschool children can be concluded to reflect any effects of ETS on the respiratory system of these children, it will be necessary to more thoroughly and more consistently consider the role of a number of potential confounding variables, both individually and in combination. It will also be necessary, before reaching such conclusions, to control and/or adjust for these factors where appropriate as well as to more consistently validate parental questionnaire-based clinical endpoints.

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Introduction

Over the past several years, we have conducted a number of analyses of the literature pertaining to the potential adverse effects of parental and/or household smoking, used as a surrogate for environmental tobacco smoke (ETS) exposure, on the respiratory system and respiratory health of children [1–5]. While an association between parental (usually maternal) smoking and prevalence of acute respiratory symptoms and certain illnesses in preschool children has been consistently reported in the literature, we found that such an association is much less consistent in studies of school-age or older children. Similarly, we have noted a lack of consistency of association between parental smoking and decreased pulmonary function in older children [1–3]. There have been no relevant studies involving pulmonary function in younger children.

As part of this ongoing analysis, we recently critically and in some detail examined the design of 45 clinical endpoint studies and 38 pulmonary function endpoint studies in school-age and older children. To assist us in this examination, a protocol was developed for the systematic extraction of information from epidemiologic studies [4]. With the aid of this protocol, we considered the following design-related aspects of the studies in question: (1) validation of clinical endpoints that had been obtained largely from parental responses to questionnaires; (2) the frequency with which 21 predetermined, potential confounding variables were considered; (3) criteria used for specific confounding variables, and (4) whether or not specific confounding variables influenced clinical and functional endpoints in these studies.

Our analysis of these studies in school-age and older children revealed that the clinical endpoints, which were usually based upon parental reporting, lacked verification (as from medical records or physician evaluation) in all but 8 of the 45 studies under consideration. In addition, most of the studies considered fewer than half of the 21 potential confounders, while the specific variables that were considered varied widely from study to study. In addition, we found that the criteria used to define a particular variable lacked standardization and varied widely from study to study, most notably for such confounding variables as socioeconomic status (SES), family size, location of residence, age of the subject, active smoking by the subject, outdoor pollution, dampness and cold, type of heating and air-conditioning and quality of housing. Several confounding variables were found to be consistently associated with increased prevalence of respiratory illness (family and personal health history or male gender) or decreased pulmonary function (personal health history, age, male gender, active smoking and location of residence) [4, 5].

In view of the inconsistencies found in studies of parental/household smoking effects in school age or older children, we initiated a similar analysis of design-related aspects of the parental/household smoking studies in preschool children. This paper reports our findings to date on this latter analysis.

Materials and Methods

The 41 studies under examination correspond to those reviewed in a previous report [3]. These studies in preschool children (0–5 years of age) deal only with clinical endpoints (i.e. the prevalence of respiratory symptoms and disease). The 21 potential confounders that were analyzed are listed in table 1. They were derived from the literature, as well as from factors considered intuitively to have a potential direct or indirect effect on the respiratory system. This list is slightly modified from that used previously in school-age children [4, 5], in order to be more relevant to this pre-school age group. Category No. 22 ('others') refers to potential confounders that differed from the 21 predetermined variables.

As indicated previously [4, 5], the studies were reviewed to determine the following information: (1) which of the potential confounders were considered; (2) what parameter(s) was (were) employed for each potential confounder; (3) whether a statistically significant association was looked for between a potential confounder and a clinical endpoint, and, if so, the direction of such an association; (4) whether there was evidence of an interaction between the potential confounder in question and other potential confounders and other variables (including parental/household smoking) that influenced the outcome of the study, and (5) whether clinical endpoints were validated by medical records or a physician's examination.

In order to facilitate the extraction of the foregoing information from the papers in question in a systematic fashion, a computer-assisted protocol was used that was slightly modified from that developed by us and described in our previous studies in school-age or older children [4, 5].

Results

General Consideration of Potential Confounders and Validation of Clinical Endpoints

As shown in table 1, most of the 21 potential confounding variables were considered in less than half of the 41 relevant studies. The only exceptions to this were (n studies): SES (34), family (26) and subject's personal health history (24), family size (23), residence location (23), age of subject (all 41) and gender (24). Other potential confounding variables were considered in very few of the studies, including indoor pollution other than that

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attributed to gas stove usage (5 studies), day care use (6), animal exposures (3), stress (1), dampness and cold (3), nutritional status of the child other than that associated with breast or artificial feeding (1) and maternal smoking during pregnancy (4). Possible exposure of the subjects to occupational contaminants and pollutants carried through the parents was considered in none of the studies. Those potential confounders designated as 'others' (item No. 22, table 1) included age of a sibling, age of parents, family composition, method of paying hospital bill, and mother working during pregnancy. Table 1 also indicates that only 21 of the 41 studies under examination validated clinical endpoints by either medical records or examination by a physician.

Table 2 displays confounder consideration for each of the studies in question and also identifies those studies in which clinical endpoints were validated. This table shows that there is a great deal of variation from one report to the other with regard to the particular array of potential confounders considered (i.e. the distribution of '+' symbols). Table 3 indicates that in all but 3 of the studies [26, 27, 39], 10 or fewer of the confounders were considered.

Detailed Information on Specific Confounding Variables

As detailed in table 4, a wide variety of criteria were used to characterize SES in the 34 studies that considered this variable. Among these were ownership of an automatic dishwasher, median or taxable income, 'social class', mother's and/or father's occupation, family living standards, mother's marital status, ethnicity, current military status, quality of home equipment (low to luxurious), frequency with which a family moved, presence in the home of both biological parents, and an SES scale based on a number of criteria. Depending upon the study, SES was based either upon a single criterion or several individual criteria.

Table 4 shows that in 10 of the studies [10, 14, 27, 28, 30, 31, 33, 39, 40, 45], no association was observed between an SES parameter and clinical endpoints, while an inverse association was found in 4 studies [19, 23, 29, 34]. One study reported that ethnicity was associated with respiratory illness, where West Indian children had a higher prevalence of chest colds compared to English/Irish or Asian children [40]. One study demonstrated an interaction between maternal work status, maternal smoking and acute respiratory illness [43]. In 8 of the studies [6, 7, 12, 17, 18, 20, 24, 35], the population was stated to have been matched or homogeneous for SES, and, therefore, no data could be provided on the association between SES and respiratory symptoms and diseases. No information on the association between SES and a clinical endpoint was provided in 11 studies that were, therefore, designated as 'none reported' [8, 9, 11, 16, 21, 22, 26, 36, 37, 41, 46]. In 22 studies [8–11, 14, 16, 19, 21–23, 26, 27, 29, 31, 33, 34, 36, 37, 39, 41, 43, 47], an association observed between parental/household smoking and the prevalence of respiratory symptoms and/or disease was adjusted for SES in some way other than that produced by matching or homogeneity.

Table 1. Frequency of consideration of potential confounders and validation of respiratory endpoints in epidemiologic studies of parental smoking and respiratory symptoms/diseases in preschool-age children

Confounder No.	Potential confounder or validation of clinical endpoint	Studies[1] (41 total)
1	SES	34
2	Gas fuel usage (cooking and heating)	12
3	Family health history	26
4	Subject's health history	24
5	Infant feeding (breast vs. bottle)	14
6	Outdoor pollution	16
7	Indoor pollution[2]	5
8	Day care use	6
9	Family size	23
10	Animal exposures	3
11	Stress	1
12	Dampness and cold	3
13	Type of heating and presence of air-conditioning	9
14	Season	18
15	Occupational exposure of subject (through parents)	0
16	Quality of housing	9
17	Nutritional status	1
18	Residence location	23
19	Age of subject	41
20	Gender of subject	24
21	Maternal smoking during pregnancy[3]	4
22	Others[4]	9
23	Validation of clinical endpoints[4]	21

[1] Number of studies in which potential confounder was considered or where clinical endpoint was validated.
[2] Other than that attributed to gas stove.
[3] As distinguished from postnatal smoking.
[4] See table 2.

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Table 2. Consideration of potential confounding variables in epidemiologic studies of parental/household smoking and respiratory symptoms/diseases in preschool-age children

Study	Reference	Confounder No.[1]																					
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Cameron et al.	6	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–
Cameron and Robertson	7	+	–	–	+	–	+	+	–	+	–	–	–	–	+	–	–	–	+	+	–	–	+[3,4]
Colley et al.	8	+	–	+	+	–	+	–	–	+	–	–	–	–	–	–	–	–	+	+	–	–	–
Harlap and Davies[2]	9	+	–	–	+	–	–	–	–	+	–	–	–	–	+	–	–	–	+	+	–	–	–
Leeder et al.[2]	10	+	–	+	–	–	+	–	–	+	–	–	–	–	–	–	–	–	+	+	+	–	+[3]
Rantakallio[2]	11	+	–	–	+	–	–	–	–	+	–	–	–	–	+	–	–	–	+	+	+	–	–
Sims et al.[2]	12	+	–	+	+	–	–	–	–	+	–	–	–	–	+	–	–	–	–	+	+	–	–
Dutau et al.[2]	13	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–
Speizer et al.[2]	14	+	+	–	–	–	+	–	–	–	–	–	–	+	–	–	–	–	+	+	+	–	–
Dutau et al.	15	–	–	+	–	–	+	–	+	–	–	–	+	+	–	–	+	–	–	+	–	–	–
Fergusson et al.[2]	16	+	–	–	+	+	–	–	–	+	–	–	–	–	+	–	–	+	+	+	–	–	+[4,5]
Pullan and Hey[2]	17	+	–	+	+	–	–	–	–	+	–	–	–	–	+	–	–	–	–	+	+	–	–
Ekwo et al.	18	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–
Schenker et al.	19	+	+	+	–	–	+	–	–	–	–	–	–	–	+	–	–	–	+	+	+	–	–
Hall et al.[2]	20	+	–	+	+	+	–	–	–	–	–	–	–	–	+	–	–	–	–	+	+	–	+[6]
Ware et al.	21	+	+	+	–	–	+	–	–	+	–	–	–	+	–	–	–	–	+	+	+	–	–
Fergusson and Horwood[2]	22	+	–	+	+	+	–	–	–	+	+	+	–	–	–	–	–	–	+	+	+	–	–
Ferris et al.	23	+	+	+	–	–	+	–	–	+	–	–	–	+	–	–	–	–	+	+	+	–	–
Pedreira et al.[2]	24	+	–	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–
Tominaga and Itoh[2]	25	–	+	+	–	–	–	+	–	–	–	–	–	+	–	–	–	–	–	+	–	–	–
Chen et al.	26	+	–	+	+	+	+	+	–	+	–	–	–	–	–	–	+	–	+	+	+	+	+[4]
McConnochie and Roghmann[2]	27	+	+	+	+	+	–	–	+	+	+	–	–	+	+	–	–	–	+	+	+	–	+[3]
Park and Kim	28	+	–	+	+	–	–	–	–	+	–	–	–	–	+	–	+	–	+	+	+	–	+[4]
Bisgaard et al.[2]	29	+	–	–	+	+	–	–	+	+	–	–	–	–	+	–	+	–	+	+	+	–	–
Cogswell et al.[2]	30	+	–	+	+	+	–	–	–	–	–	–	–	–	+	–	–	–	–	+	–	–	–
Fleming et al.	31	+	–	+	–	+	–	–	+	+	–	–	–	–	+	–	–	–	–	+	+	–	–
Geller-Bernstein et al.[2]	32	–	–	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–
Kershaw[2]	33	+	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–
Ogston et al.[2]	34	+	+	–	–	+	–	–	–	+	–	–	–	+	–	–	–	–	–	+	–	–	+[4,7]
Salzman et al.[2]	35	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–
Stern et al.	36	+	+	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–
Taylor and Wadsworth	37	+	–	–	+	+	–	–	–	+	–	–	–	–	+	–	+	–	–	+	–	+	–
Toyoshima et al.[2]	38	–	–	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–
Chen et al.	39	+	+	+	+	+	+	+	+	+	–	–	–	–	+	–	+	–	+	+	+	+	+[3]
Marks	40	+	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–
Chen	41	+	–	–	+	+	+	–	–	–	–	–	–	–	+	–	–	–	+	+	+	+	–
Murray and Morrison	42	–	+	+	+	–	–	+	–	–	+	–	–	+	–	–	–	–	–	+	+	–	–
Ostro	43	+	–	+	+	–	+	–	–	+	–	–	+	–	+	–	–	–	+	+	+	–	–
Harsten et al.[2]	44	–	–	+	–	–	+	–	+	+	–	–	–	–	+	–	+	–	+	+	+	–	–
Ross et al.[2]	45	+	+	+	+	–	–	–	–	+	–	–	+	+	–	–	+	–	+	+	–	–	–
Weitzman et al.	46	+	–	–	–	–	–	–	–	+	–	–	–	–	–	–	+	–	–	+	+	–	–

+ = Indicates that potential confounding variables were considered in a particular study.

1 Corresponds to numbers in table 1.

2 Clinical endpoints verified.

3 Age of sibling.

4 Age of parent.

5 Family composition.

6 Method of paying hospital bill.

7 Mother working during pregnancy.

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Table 3. Number of individual potential confounders considered in each of the epidemiologic studies

Study	Reference	Confounders considered (out of a possible 22[1])
Cameron et al.	6	4
Cameron/Robertson	7	9
Colley et al.	8	7
Harlap/Davies	9	6
Leeder et al.	10	8
Rantakallio	11	7
Sims et al.	12	7
Dutau et al.	13	1
Speizer et al.	14	7
Dutau et al.	15	7
Fergusson et al.	16	9
Pullan and Hey	17	7
Ekwo et al.	18	4
Schenker et al.	19	8
Hall et al.	20	8
Ware et al.	21	9
Fergusson and Horwood	22	10
Ferris et al.	23	9
Pedreira et al.	24	5
Tominaga and Itoh	25	5
Chen et al.	26	13
McConnochie and Roghmann	27	14
Park and Kim	28	10
Bisgaard et al.	29	10
Cogswell et al.	30	6
Fleming et al.	31	8
Geller-Bernstein et al.	32	4
Kershaw	33	5
Ogston et al.	34	7
Salzman et al.	35	3
Stern et al.	36	6
Taylor and Wadsworth	37	8
Toyoshima et al.	38	4
Chen et al.	39	16
Marks	40	3
Chen	41	9
Murray and Morrison	42	8
Ostro	43	10
Harsten et al.	44	9
Ross et al.	45	10
Weitzman et al.	46	5

[1] As listed in table 1.

Table 5 details the treatment of family health history as a potential confounding variable. Among the criteria used for this variable were: parental respiratory disability based upon morning phlegm production in winter; sibling respiratory symptoms and diseases; family history of atopy and wheezing; parental cough; exclusion of subjects on the basis of a disturbed family background; history of wheeze in first degree relatives; parental history of bronchitis, emphysema and asthma; history of asthma, allergic rhinitis and eczema in parents and siblings; adult chronic respiratory disease in the family; number of sick children in the household; family history of acute otitis media, and recent family history of respiratory infection.

Table 5 shows that in 6 of the studies [12, 17, 18, 20, 31, 38], no association was observed between family health history and clinical endpoints, while a direct association was observed in 12 studies [8, 10, 15, 19, 21, 23–25, 27, 28, 33, 43]. A possible interaction was noted between maternal smoking and family health history in 1 study [25]. In 2 studies [30, 42], the population was matched or considered homogeneous for family health history and, thus, provided no data on associations. In 6 studies [22, 26, 36, 39, 44, 45], no information regarding associations of the endpoint and family health history was provided ('none reported'). In 12 studies [8, 10, 18, 19, 21–23, 26, 27, 36, 39, 43], the observed association between parental smoking and prevalence of respiratory symptoms and diseases in children was adjusted for family health history in some way other than that produced by homogeneity or matching.

Details regarding the treatment of personal health history as a potential confounder are provided in table 6. Among the specific criteria for this potential confounder were illness in the past year, birth weight, birth order, history of respiratory syncytial virus (RSV) bronchiolitis or RSV infection, gestational age, perinatal status, early eczema, early respiratory illness, birth interval, atopic history, body fluid immunoglobulins, history of lower respiratory tract infections, history of hospital admissions for chest problems, pertussis immunization status, eosinophilia history, and previous attacks of acute otitis media. While no association with respiratory symptoms and diseases was observed in 4 studies [16, 26, 33, 38], a direct association was found in 8 studies [9, 17, 20, 22, 29, 30, 32, 38]. An interaction between low birth weight, other variables and household smoking is suggested in another study [39]. No data could be provided on associations relative to this variable in 5 studies [6, 7, 12, 27, 42] because populations were either matched or considered homogeneous. No information on the influence of personal health history on respiratory illness was reported in 6 of the studies [8, 28, 37, 41, 43, 45]. In 8 studies that reported an association between parental/household smoking and clinical endpoints [8, 9, 30, 32, 37, 39, 40, 43], adjustment was made for personal health history of the subject in some way other than that of matching and homogeneity.

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Table 4. Consideration of SES in the epidemiologic studies

Study	Reference	Parameter(s)	Associations
Cameron et al.	6	automatic dishwasher	NA (matched)
Cameron and Robertson	7	median yearly income	NA (matched)
Colley et al.	8	social class	none reported
Harlap and Davies	9	husband's occupation	none reported
Leeder et al.	10	father's occupation	none observed
Rantakallio	11	father's occupation; taxable income of families; matched for marital status of mother	none reported
Sims et al.	12	social class based on occupation	NA (matched)
Dutau et al.	13	none	NA
Speizer et al.	14	educational attainment and occupation of both parents	none observed
Dutau et al.	15	none	NA
Fergusson et al.	16	education; family living standards; maternal ethnic status; family income	none reported
Pullan and Hey	17	social class	NA (matched)
Ekwo et al.	18	subjects were from middle and upper social classes	NA (homogeneous)
Schenker et al.	19	SES scale based on parental occupation and education; sample was 98% white	severe chest illness before 2 years of age inversely related to SES
Hall et al.	20	cases and controls matched for race	NA (matched)
Ware et al.	21	parental occupation and education; Green SES scale based on income, occupation, ethnicity and maternal education	none reported
Fergusson and Horwood	22	Elley and Irving scale (which incorporates maternal age, family size, maternal educational level, children's ethnicity, and social and economic status of family)	none reported
Ferris et al.	23	three levels of SES based on mean number of years of schooling of the parents	respiratory illness before the age of 2 years is inversely related to SES
Pedreira et al.	24	89% of subjects were white	NA (homogeneous)
Tominaga and Itoh	25	none	NA
Chen et al.	26	family income; father's education	none reported
McConnochie and Roghmann	29	subject population primarily composed of white middle-class families; dichotomous SES index based upon level of maternal education	none observed
Park and Kim	28	father's occupation; parental education; economic status (upper, middle, lower)	none observed

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Table 4 (continued)

Study	Reference	Parameter(s)	Associations
Bisgaard et al.	29	social status scale based on occupation, salary, education, and type of living accommodation	low social status score a risk factor for wheeze in infancy
Cogswell et al.	30	social class	none observed
Fleming et al.	31	ethnicity; family income	none observed
Geller-Bernstein et al.	32	none	NA
Kershaw	33	civilian vs. armed service	none observed
Ogston et al.	34	father's employment (manual vs. nonmanual)	respiratory and alimentary illnesses inversely related to social class
Salzman et al.	35	matched for ethnicity	NA (matched)
Stern et al.	36	study locales of similar demographic and economic profiles; adjusted for parental education	none reported
Taylor and Wadsworth	37	assessment of home equipment by health visitor (luxurious, high, average, low, very low standard); number of times family moved during child's life; social index (based on domestic crowding, parental education, tenure of accommodation, type of neighborhood, parental occupation)	none reported
Toyoshima et al.	38	none	NA
Chen et al.	39	father's educational status (university, secondary, primary); average living costs per capita	none observed
Marks	40	ethnicity (English/Irish, Asian, West Indian)	none observed for wheezing, coughing; West Indian children had significantly higher incidence of chest colds
Chen	41	annual income; father's education (university, secondary, primary)	none reported
Murray and Morrison	42	none	NA
Ostro	43	education of head of household; family income; work status of mother; ethnicity	positive interaction between maternal smoking and nonworking mother and acute respiratory illness
Harsten et al.	44	none	NA
Ross et al.	45	social class based upon occupation; number of parents/adults in house	none observed
Weitzman et al.	46	race; presence of both biological parents; family income; maternal education (less than high school, high school, college)	none reported

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Table 5. Consideration of family health history in the epidemiologic studies

Study	Reference	Parameter(s)	Associations
Cameron et al.	6	none	NA
Cameron and Robertson	7	none	NA
Colley et al.	8	parental respiratory disability based upon morning phlegm production in winter	incidence of bronchitis and pneumonia at 1 year of age associated with parental symptoms; association disappears at 2–5 years
Harlap and Davies	9	none	NA
Leeder et al.	10	parents (morning phlegm in winter; asthma-wheeze); siblings (cough-phlegm, bronchitis, pneumonia, colds, whooping cough, etc.)	incidence of bronchitis and pneumonia at 1 year of age associated with parental asthma-wheeze and sibling bronchitis and pneumonia; incidence of upper respiratory illness (bad colds) at 1 year of age associated with parental cough-phlegm and sibling bronchitis and pneumonia
Rantakallio	11	none	NA
Sims et al.	12	family history of atopy and wheezing	none observed
Dutau et al.	13	none	NA
Speizer et al.	14	none	NA
Dutau et al.	15	parental coughing	parental coughing associated with coughing in children
Fergusson et al.	16	none	NA
Pullan and Hey	17	exclusion of subjects on the basis of disturbed family background; history of wheeze in first degree relatives	none observed
Ekwo et al.	18	parental respiratory history	none observed
Schenker et al.	19	parental respiratory and allergic history	parental history associated with severe chest illness in children <2 years of age
Hall et al.	20	family history of atopy (allergic rhinitis, asthma)	none observed
Ware et al.	21	history of bronchitis, emphysema, or asthma of either parent	parental history strong risk factor for respiratory illness in children <2 years of age
Fergusson and Horwood	22	history of asthma, allergic rhinitis, and eczema in parents and siblings	none reported
Ferris et al.	23	history of bronchitis, emphysema, or asthma of either parent	parental history of respiratory illness associated with respiratory illness <2 years of age
Pedreira et al.	24	family history of chronic cough, chronic bronchitis, asthma, other respiratory illness	family history of cough and bronchitis are associated with increased bronchitis (but not tracheitis) in infants; family history of asthma or other respiratory illnesses not associated with bronchitis or tracheitis in infants
Tominaga and Itoh	25	family history of cough and sputum	associated with common colds (but not asthmatic bronchitis) in 3-year-olds; possible interaction with maternal smoking for asthmatic bronchitis
Chen et al.	26	adult cases of chronic respiratory disease in family	not reported

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Table 5 (continued)

Study	Reference	Parameter(s)	Associations
McConnochie and Roghmann	27	history of hay fever (and/or allergic rhinitis) or asthma in parents and/or siblings	family history of asthma (but not allergy) risk factor for bronchiolitis
Park and Kim	28	cough and phlegm in household	cough in household associated with cough in children
Bisgaard et al.	29	none	NA
Cogswell et al.	30	all children had a parental history of asthma or hay fever	NA (homogeneous)
Fleming et al.	31	number of children sick within household	none observed
Geller-Bernstein et al.	32	none	NA
Kershaw	33	family history of atopic symptoms in first degree relatives	predictor of asthma
Ogston et al.	34	none	NA
Salzman et al.	35	none	NA
Stern et al.	36	history of chronic respiratory illness in either parent	none reported
Taylor and Wadsworth	37	none	NA
Toyoshima et al.	38	major allergy (atopic dermatitis, asthma, rhinitis, recurrent urticaria) and minor allergy (adverse drug reaction) in relatives	none observed
Chen et al.	39	adult history of chronic respiratory disease	none reported
Marks	40	none	NA
Chen	41	none	NA
Murray and Morrison	42	exposed and nonexposed children comparable with regard to family history of asthma	NA (matched)
Ostro	43	parental respiratory illness	significantly associated with days children spent in bed due to respiratory illness
Harsten et al.	44	family history of allergy (eczema, asthma, hay fever, nettle rash, drug allergy) and acute otitis media	none reported
Ross et al.	45	recent family history of respiratory infection	none reported
Weitzman et al.	46	none	NA

As shown in table 7, the following specific criteria were used to characterize infant feeding as a confounding variable: early infant diet; presence or absence of breast feeding; duration of breast feeding; method of infant feeding (breast, mixed, artificial); time of initiation of formula, whole milk and solid food; age of weaning, and formula use after 1 month of age. No association between the endpoint and infant feeding was observed in 7 studies [20, 27, 29, 30, 31, 34, 38]. A direct association between artificial feeding and increased prevalence of respiratory symptoms and/or certain diseases in children (or an inverse relationship of the endpoint with breast feeding) was noted in 2 studies [26, 32]. In 2 studies, infant feeding appeared to interact with other confounding variables and/or household smoking [39, 41]. No information pertaining to an association between this variable and endpoints was reported in 3 studies [16, 22, 37]. The association between parental/household smoking and prevalence

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Table 6. Consideration of subject's personal health history in the epidemiologic studies

Study	Reference	Parameter(s)	Associations
Cameron et al.	6	no difference between exposed and nonexposed subjects with regard to illness within the past year	NA (matched)
Cameron and Robertson	7	stated that most of the children were not ill	NA (homogeneous)
Colley et al.	8	subjects from multiple births excluded from study; birth weight	none reported
Harlap and Davies	9	birth weight; birth order	admission rates for respiratory illnesses are elevated in infants with low birth weights
Leeder et al.	10	none	NA
Rantakallio	11	birth order of exposed and nonexposed subjects matched	NA
Sims et al.	12	cases (RSV bronchiolitis) and controls matched for birth weight and atopic history	NA (matched)
Dutau et al.	13	none	NA
Speizer et al.	14	none	NA
Dutau et al.	15	none	NA
Fergusson et al.	16	birth weight; gestational age	none observed
Pullan and Hey	17	subjects excluded from the study on the basis of physical handicap (spina bifida, tracheoesophageal fistula, cyanotic congenital heart disease, myopathy, leukemia) severe enough to interfere with assessment; history of RSV infection during 1st year of life	RSV infection associated with wheeze at 0–4 years of age
Ekwo et al.	18	none	NA
Schenker et al.	19	none	NA
Hall et al.	20	subjects were excluded from the study on the basis of underlying disease other than RSV; age of hospitalization for RSV lower respiratory tract disease	younger age ($\leq$ 12 weeks) at time of hospitalization for RSV disease associated with lower arterial O_2 at 4–5 years of age
Ware et al.	21	none	NA
Fergusson and Horwood	22	perinatal status (birth weights, gestational ages) early eczema; early respiratory illness	respiratory illness at 0–2 years of age associated with same at 2–4 and 4–6 years of age
Ferris et al.	23	none	NA
Pedreira et al.	24	none	NA
Tominaga and Itoh	25	none	NA
Chen et al.	26	birth weight; relatively few (2–3%) multiple births; children excluded on basis congenital heart disease and death before 18 months of age	none observed for birth weight

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Table 6 (continued)

Study	Reference	Parameter(s)	Associations
McConnochie and Roghmann	27	cases (bronchiolitis) and controls excluded for medical abnormalities (premature birth, cardiac anomaly, neuromuscular disorder, esophageal atresia)	NA (homogeneous)
Park and Kim	28	birth order; birth interval	none reported
Bisgaard et al.	29	birth weight	low birth weight (<2,500 g) associated with increased wheezing during the 1st year of life
Cogswell et al.	30	atopic history (eczema or skin prick test); body fluid IgE and IgA	atopic history associated with wheezing in children; IgE (but not IgA) associated with wheeze
Fleming et al.	31	none	NA
Geller-Bernstein et al.	32	history of lower respiratory tract infections; blood IgE; all were atopic by skin test	history of respiratory illness negatively correlated with recovery of persistent wheeze; none observed for IgE
Kershaw	33	previous hospital admissions for chest problems; pertussis immunization status; chest deformity; evidence of atopy and/or atopic potential; serum IgE	none observed for IgE and pertussis immunization, and chest deformity; none reported hospitalization history
Ogston et al.	34	none	NA
Salzman et al.	35	none	NA
Stern et al.	36	none	NA
Taylor and Wadsworth	37	birth weight; birth order	none reported
Toyoshima et al.	38	serum IgE; eosinophilia history (and age of initial wheezing); allergic history (eczema, allergic rhinitis, recurrent urticaria, food allergy); disturbances at birth; fever with wheezing	eosinophilia found in asthmatic infants more than in nonasthmatic infants; age of initial wheezing in asthmatic infants significantly older than in nonasthmatic infants; none observed for other variables
Chen et al.	39	preterm birth; birth weight	low birth weight (along with artificial feeding and male gender) may enhance association between household smoking and hospitalization due to respiratory illness during the first 18 months of life
Marks	40	none	NA
Chen	41	birth weight; multiple births	none reported
Murray and Morrison	42	all asthmatics; exposed and nonexposed matched for number and duration of colds, atopy (by skin test); size of mite reaction larger in exposed than in nonexposed subjects	NA (matched)
Ostro	43	existence of chronic health conditions	none reported
Harsten et al.	44	none	NA
Ross et al.	45	number of previous attacks of acute otitis media	none reported
Weitzman et al.	46	none	NA

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Table 7. Consideration of breast versus bottle feeding of infants in the epidemiologic studies

Study	Reference	Parameter(s)	Associations
Fergusson et al.	16	early infant diet	none reported
Hall et al.	20	breast feeding	none observed
Fergusson and Horwood	22	presence, absence and duration of breast feeding	none reported
Chen et al.	26	method of infant feeding (breast or mixed vs. artificial)	artificial feeding predictor of hospital admissions for respiratory infections in children ≤ 18 months
McConnochie and Roghmann	27	breast feeding (occurrence and duration) and time of initiation of formula, whole milk and solid food	none observed
Bisgaard et al.	29	age of weaning from breast	none observed
Cogswell et al.	30	duration of breast feeding	none observed
Fleming et al.	31	breast feeding in children <6 months of age	none observed
Geller-Bernstein et al.	32	breast feeding	inversely associated with persistence of wheeze
Ogston et al.	34	bottle vs. breast feeding	none observed upon regression analysis
Taylor and Wadsworth	37	breast feeding	none reported
Toyoshima et al.	38	use of formula after 1 month of age	none observed
Chen et al.	39	breast/mixed feeding vs. artificial feeding	artificial feeding (along with male gender and low birth weight) may enhance association between household smoking and hospitalization due to respiratory illness during the first 18 months of life
Chen	41	breast/mixed feeding vs. artificial feeding	artificial feeding enhanced dose-response relationship between household smoking and incidence of hospitalization due to respiratory illness during the first 18 months of life

of respiratory symptoms and disease in preschool children was adjusted for infant feeding in some way other than by matching or homogeneity in 4 studies [16, 22, 26, 37].

As detailed in table 8, the specific criteria for day care use were: home care vs. day care and kindergarten; day care outside the home; and home care vs. family care vs. a day-care center. The population was considered homogeneous for this variable in 1 study [27] and was omitted from the regression model in another [39]. A direct association between day care and the prevalence of respiratory symptoms and/or disease was reported in 4 studies [5, 29, 31, 44]. The observed association between parental household smoking and endpoint was adjusted for this variable in 2 studies [29, 31].

Table 9 provides details on 4 potential confounding variables: (a) gas fuel usage; (b) indoor pollution other than gas fuel usage; (c) dampness and cold, and (d) type of heating and air-conditioning. The criteria used for gas fuel usage were gas fuel usage, gas cooking fuel, cooking stoves, home cooking fuel, and gas for cooking and heating. This variable was matched in 1 study [42]. No association for gas fuel usage and the endpoint was observed in 4 studies [19, 21, 25, 34], while gas fuel use was associated with the prevalence of respiratory symptoms and disease in 3 studies [4, 18, 45]. No information regarding associations of the endpoint and gas fuel usage was reported in 4 studies [23, 27, 36, 39]. The observed association between parental/household smoking and incidence of respiratory illness was adjusted for gas fuel usage

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Table 8. Consideration of day care use in the epidemiologic studies

Study	Reference	Parameter(s)	Associations
Dutau et al.	15	home care vs. day care and kindergarten	respiratory index (rating based upon 6 parameters of respiratory illness) elevated in children (1 month–6 years) who go to day care or kindergarten compared to those cared at home
McConnochie and Roghmann	27	none of the subjects were in day care during the study period (first 2 years of life)	NA (homogeneous)
Bisgaard et al.	29	day care outside of the home	day care outside of the home associated with increased wheezing during the 1st year of life
Fleming et al.	31	day care (defined as supervised care of at least 2 unrelated children (>4 h/week))	associated with increased upper respiratory infection and ear infection in children <5 years of age
Chen et al.	39	use of day care	omitted from regression model
Harsten et al.	44	home care vs. family day care (4–6 children) vs. day care centers (10–12 children)	select forms of respiratory tract infection elevated in 2- and 3-year olds attending day care centers relative to family day care and home care

in 2 studies [6, 25]. A potential interaction between parental smoking and this variable was reported in another study [18] (table 9).

The criteria used for indoor pollution other than gas stove usage were: ventilation problems; quality of ventilation; kerosene stove; ventilated heater; coal for cooking, and woodstove emissions. Two studies were matched for indoor pollution [7, 42]. No association with the endpoint was observed in 1 study [25], and no information on an association was reported in 2 studies [26, 39]. The observed association between parental smoking and the endpoint was adjusted for indoor pollution in 1 study [25] (table 9).

The criteria used for dampness and cold were: cold temperature; relative humidity; temperature in the bedroom and living room; the absence of a radiator in the bedroom, and minimum winter temperature. No association was observed for cold in 1 study [15], while in another study respiratory illness in children was associated with cooler, more humid bedrooms [45]. No information concerning associations attributable to this variable was available in 1 study [43]. In this particular study, the effect associated with ETS was adjusted for this variable [43] (table 9).

The specific criteria used for type of heating and air-conditioning were: type of heating (oil, gas, electric); heating fuel and air-conditioning; presence of an air conditioner; home heating methods; wood stove use, and gas vs. central heating. This potential confounding variable was matched in 1 study [42]. No association between this variable and endpoint was observed in 3 studies [14, 21, 23]; while an association was observed in 4 studies [15, 25, 34, 45]. No information regarding an association was available in 1 study [27]. An observed association between parental smoking and the endpoint was adjusted for this variable (other than by matching) in 1 study [34] (table 9).

Table 10 deals with the treatment of gender as a potential confounding variable. This variable was matched in 1 study [12]. No association between gender and respiratory illness was observed in 5 studies [19, 28, 31, 32, 44], while in 8 studies [10, 17, 21, 23, 27, 29, 33, 41], male gender was associated with increased prevalence of respiratory illness. An interaction between male gender and other variables and household smoking was suggested in 1 study [39]. In no study was such an association found for female gender. No information was available for gender as a potential variable in 9 studies [6, 11, 14, 20, 22, 26, 42, 43, 46]. Observed associations between parental/household smoking and respiratory illness were adjusted for gender (other than by matching) in 5 studies [10, 21, 29, 41, 42].

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Table 9. Consideration of gas fuel usage, indoor pollution, dampness and cold, and type of heating and presence of air-conditioning in the epidemiologic studies

Study	Reference	Parameter(s)	Associations
Cameron and Robertson	7	B) percent reporting ventilation problems similar for exposed vs. nonexposed households	NA (matched)
Speizer et al.	14	A) gas fuel usage (monitored mass respirable particles and NO_2) D) type of heating (oil, gas, electric)	A) associated with serious respiratory illness before age of 2 years D) none observed
Dutau et al.	15	C) cold temperature D) collective vs. individual heating	C) none observed D) collective heating associated with increased respiratory illness
Ekwo et al.	18	A) gas cooking fuel	A) associated with increased risk of hospitalization for respiratory illness before 2 years of age
Schenker et al.	19	A) cooking stove fuel (gas electric or other)	A) none observed
Ware et al.	21	A) use of gas cooking D) heating fuel and air-conditioning	A) none observed D) dropped from regression analysis because it did not figure into regression
Ferris et al.	23	A) use of gas cooking D) heating fuel and air-conditioning	A) none reported D) dropped from regression analysis because it did not figure into regression
Tominaga and Itoh	25	A) gas stoves B) kerosene stove, electric stove, ventilated heater D) air conditioner	A) none observed B) none observed D) associated with increased common colds in 3-year olds
Chen et al.	26	B) coal used for cooking	B) none reported
McConnochie and Roghmann	27	A) home cooking fuel D) home heating methods	A) none reported D) none reported
Ogston et al.	34	A) gas cooking and heating D) type of heating (e.g. coal, gas, electric, etc.)	A) none observed for gas cooking D) respiratory illness during 1st year of life associated with type of heating (gas and electric > central storage and coal)
Stern et al.	36	A) gas cooking in the home	A) none reported
Chen et al.	39	A) cooking fuel (coal, gas) B) ventilation in home (good, fair, bad)	A) none reported B) none reported
Murray and Morrison	42	A) exposed and nonexposed children were comparable for gas stove usage B), D) exposed and nonexposed children were comparable for emissions for woodstove use for heating	A) NA (matched) B), D) NA (matched)
Ostro	43	C) winter minimum temperature	none reported
Ross et al.	45	A) gas use for heating and cooking C) mean relative humidity and temperature in bedroom and living room; central heating radiator vs. no heating in child's bedroom D) gas vs. central heating	A) see D) C) upper respiratory infection in children 3–5 years old associated with cooler bedrooms and higher relative humidity D) wheezing associated with gas vs. central heating in children 3–5 years old

A) = Gas fuel usage; B) = indoor pollution; C) = dampness/cold; D) = type of heating/presence of air-conditioning.

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Table 10. Consideration of gender in the epidemiologic studies

Study	Reference	Parameter(s)	Associations
Cameron et al.	6	exposed and nonexposed children matched for gender	none reported
Leeder et al.	10	gender	bronchitis/pneumonia of males > females in children < 5 years of age
Rantakallio	11	exposed and nonexposed children matched for gender	none reported
Sims et al.	12	cases (RSV bronchiolitis) and controls matched for gender	NA (matched case-control)
Speizer et al.	14	gender	none reported
Pullan and Hey	17	cases (RSV infection) and controls matched for gender	episodes of wheeze in boys > girls (0–2 years); none observed for recurrent wheeze
Schenker et al.	19	gender	none observed for chest illness in children < 2 years of age
Hall et al.	20	cases (RSV infection) and controls matched for gender	none reported
Ware et al.	21	gender	males > females for respiratory illness before 2 years of age
Fergusson and Horwood	22	gender	none reported
Ferris et al.	23	gender	males > females for respiratory illness before 2 years of age
Chen et al.	26	gender	none reported
McConnochie and Roghmann	27	cases (bronchiolitis) and controls matched for gender	incidence of bronchiolitis up to 2 years of age in males > females
Park and Kim	28	gender	none observed
Bisgaard et al.	29	gender	incidence of wheezing at 1 year of age in males > females
Fleming et al.	31	gender	none observed
Geller-Bernstein et al.	32	gender	none observed
Kershaw	33	gender	majority of asthmatics ≤ 3 years of age were males
Chen et al., 1988	39	gender	male gender (along with low birth weight and artificial feeding) may enhance association between household smoking and hospitalization due to respiratory illness during the first 18 months of life
Chen	41	gender	frequency of hospitalization due to respiratory illness at 18 months of age in males > than females
Murray and Morrison	42	gender	none reported
Ostro, 1989	43	gender	none reported
Harsten et al., 1990	44	gender	none observed
Weitzman et al., 1990	46	gender	none reported

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Table 11. Consideration of age of the subject in the epidemiologic studies

Study	Reference	Parameter(s)	Associations
Cameron et al.	6	< 16, < 9 and < 5 years of age	no age analysis within preschool-age group
Cameron and Robertson	7	0–5, 6–9, 10–16 years of age	no age analysis within preschool-age group
Colley et al.	8	0–5 years, longitudinal study	association between bronchitis and pneumonia in children and parental smoking or parental phlegm disappears by 2 years of age
Harlap and Davies	9	age in months during 1st year of life	association between smoke exposure and admission rates for bronchitis/pneumonia observed at 6–9 months but not 0–5 months of age
Leeder et al.	10	1st year of life	NA (homogeneous)
Rantakallio		compared subjects < 1 year of age with those 1–5 years of age	the 'dose-response' relationship between maternal smoking and respiratory diseases in children < 1 year of age was not demonstrable in children 1–5 years old (although maternal smoking association observed for both age groups)
Sims et al.	12	1st year of life	NA (homogeneous)
Dutau et al.	13	compared those children aged 1–12 months with total group < 6 years of age	at 1–12 months of age prevalence of chronic cough less than, while prevalence of asthmatoid bronchitis, rhinopharyngitis, and laryngitis more than total group (all children were smoke-exposed with no unexposed control children); total number of children is small (n = 40)
Speizer et al.	14	respiratory illness in children < 2 years old was one of the endpoints	NA (homogeneous)
Dutau et al.	15	1 month–6 years of age	no age comparisons within this age group
Fergusson et al.	16	1, 2, 3 years of age	association between maternal smoking and bronchitis/pneumonia disappears by 3 years of age
Pullan and Hey	17	10-year longitudinal study; history of wheeze from 0–4 years of age was an endpoint	no age comparison within this age group
Ekwo et al.	18	hospitalization for respiratory illness before age 2 was one of the endpoints	NA (homogeneous)
Schenker et al.	19	severe chest illness prior to 2 years of age was one of the endpoints	NA (homogeneous)
Hall et al.	20	8-year longitudinal study of subsequent effects of infantile RSV infection	no age comparison within preschool-age group
Ware et al.	21	respiratory illness before 2 years of age was one of the endpoints	NA (homogeneous)
Fergusson and Horwood	22	6-year longitudinal study	rates of respiratory symptoms and illness higher in children 0–2 years old compared to those 2–6 years of age; association between maternal smoking and lower respiratory symptoms and infection in children disappeared after 2 years of age
Ferris et al.	23	respiratory illness before 2 years of age was one of the endpoints	NA (homogeneous)
Pedreira et al.	24	1st year of life	NA (homogeneous)
Tominaga and Itoh	25	all children 3 years of age	NA (homogeneous)
Chen et al.	26	0–18 months of age	NA (homogeneous)

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Table 11 (continued)

Study	Reference	Parameter(s)	Associations
McConnochie and Roghmann	27	cases (bronchiolitis) and controls matched for age; retrospective study involving all children < 2 years of age	NA (matched and homogeneous)
Park and Kim	28	0–14 years of age	no separate evaluation within preschool-age group
Bisgaard et al.	29	1st year of life	NA (homogeneous)
Cogswell et al.	30	longitudinal study in children 0–5 years of age with a genetic predisposition to allergic disease	majority (69%) of children had 1st episode of wheezing by 2 years of age; during the 1st year of life ingested allergen accounted for most of the (+) atopic reactions in children with eczema while at age 5 inhalant allergens were the predominant cause of (+) atopic reaction in children with eczema; parental smoking associated with wheeze at 5 years of age but not at 1 year of age
Fleming et all	31	0–5 years of age (comparison above and below 36 months of age)	children < 36 months were at greater risk of ear infection than children > 36 months old; household crowding increases risk of upper respiratory tract infection in children < 36 months old
Geller-Bernstein et all	32	≤ 5 years of age	no age comparisons in this group
Kershaw	33	≤ 6 years of age	no age comparison in this group
Ogston et al.	34	within 1st year of life	NA (homogeneous)
Salzman et al.	35	cases (croup) and controls matched for age; children < 5 years old vs. children < 1 year old	none reported
Stern et al.	36	hospitalization for chest illness before the age of 2 was one of the endpoints	NA (homogeneous)
Taylor and Wadsworth	37	0–5 years of age, all subjects born at the same time; comparison of hospital admission for lower respiratory illness at 0–12, 12–35 and 35–59 months	association between maternal smoking and hospital admissions for lower respiratory illness greatest at 0–12 months of age
Toyoshima et al.	38	0–3 years of age; average age between cases (asthma) and 2 sets of controls (wheezy, nonwheezy) were not significantly different	matched; however, initial age of wheezing for asthma group was significantly later than for controls
Chen et al.	39	0–18 months of age; comparison of infants 0–6 months old with those 7–18 months old	association between household smoking and incidence of hospitalization due to respiratory illness declines at 7–18 months compared to 0–6 months of age
Marks	40	all children 4.5–5 years of age	NA (homogeneous)
Chen	41	0–18 months of age	NA (homogeneous)
Murray and Morrison	42	one of the age groups compared for asthma severity was 1–6 years of age	no comparison made within this age group
Ostro	43	0–6 years of age; adjusted for age	none reported
Harsten et al.	44	0–3 years of age; endpoints analyzed on the basis of quarters	selected respiratory diseases and ear infection more prevalent during year 2 than years 1 and 3; incidence of acute tonsillitis greater in years 2 and 3 than year 1; see table 8 for additional age-related associations
Ross et al.	45	3–5 years of age	NA (homogeneous)
Weitzman et al.	46	0–5 years of age; examined asthma onset at 1 year and 2–5 years	none reported

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Table 11 shows that a wide variation of age ranges (i.e. 0–3, 0–4, 0–5, 0–6 and 0–14 years, <1 year, <2 years, 1 month–6 years, 3 years of age and 4.5–5 years) and age comparisons (i.e. 0–5 vs. 6–9 months, 1–12 months vs. <6 years, 0–2 vs. 2–6 years, above and below 36 months, <1 vs. <5 years) were considered in the 41 relevant studies. Ages were matched or subjects were homogeneous for age in 17 studies [10, 12, 14, 18, 19, 21, 23–25, 27, 29, 34, 36, 38, 40, 41, 45]. An association between age and the endpoint was observed in 7 studies [11, 13, 22, 30, 31, 38, 44]. Of these, prevalence of respiratory illness and disease was inversely associated with age in 5 studies [13, 22, 31, 38, 44] and directly associated with age in 3 studies [13, 30, 44]. A biphasic age-related association was found in 2 studies [13, 44]. An interaction between age and day care use is suggested in 1 study [42], while another study suggests an interaction between age and crowding [31]. An interaction between age and parental/household smoking is suggested in six studies [8, 9, 11, 16, 37, 39], with all but 1 [9] showing that this association diminished with age. No information regarding an association between age and end point was provided in 12 studies [6, 7, 15, 17, 20, 28, 32, 33, 35, 42, 43, 46]. In 5 studies where an association between parental/household smoking and respiratory symptoms and illness was reported [8, 22, 31, 37, 38], adjustment was made for age of the subject other than by matching or homogeneity. In 1 study [30], an interaction was suggested between parental smoking, age and wheeze.

The population was matched or considered homogeneous for season as a potential confounding variable in 11 studies [7, 12, 16, 17, 19, 20, 27, 31, 37, 39, 41] (data not shown). Season was associated with clinical endpoints in 3 studies [9, 11, 43] where the prevalence of respiratory illness was greater in winter than at other times of year. In 1 study [30], no association was observed for this variable. In 1 study [29], the risk of wheezing during the first year of life was greater for children born during April–September (spring–fall) than those born during October–March (fall–winter) [29], while in another study, no association was seen for season of birth [30]. In 1 study [43], no information was provided regarding associations between season and respiratory illness. Three studies [9, 11, 29] suggested that season or season of birth has little or no influence on the association between parental/household smoking and endpoint (data not shown).

Table 12 summarizes the associations between the foregoing potential confounding variables and the clinical endpoints in these studies. As can be seen from the table, there was an association between the potential confounder and symptoms and/or illness prevalence in a majority of the studies relative to family health history (12 of 18 studies), age (5 of 6), gender (8 of 13), personal health history (8 of 12), day care use (4 of 4) and season (3 of 4). On the other hand, a majority of the studies observed no association relative to SES (10 of 14 studies), artificial feeding (7 of 9) and gas fuel use and indoor pollution other than gas fuel (5 of 8). In the case of dampness and cold and heating/air-conditioning, the data were inconclusive.

Table 12. Associations between potential confounding variables and clinical endpoints in the epidemiologic studies

Increased/decreased prevalence of symptoms/illness[1]
Family health history (+, 12/18 studies)
Age (–, 5/6 studies)
Gender (+ males, 8/13 studies)
Personal health history (+ 8/12 studies)
Day care use (+, 4/4 studies)
Season (+ winter, 3/4 studies)
No association observed[2]
SES (10/14 studies)
Artificial feeding (7/9 studies)
Gas fuel use/indoor pollution (5/8 studies)
Association equivocal[3]
Dampness and cold (+1 study, no association 1 study)
Heating/air-conditioning (+4 studies, no association 3 studies)

[1] Number of studies with increased (+) or decreased (–) prevalence/total number of studies addressing potential confounder, excluding studies in which groups were homogeneous or the variable was matched or associations not reported.

[2] Number of studies in which no association observed/total number of studies addressing potential confounder, excluding studies in which the groups were homogeneous or the variable was matched or association not reported.

[3] + = increased prevalence of symptoms/illnesses associated with variable.

Discussion

In this analysis, we used basically the same systematic protocol employed previously in studies of school-age children to extract information from epidemiologic studies of parental smoking and respiratory health in preschool children. Only 2 modifications were implemented. Confounder No. 21 in the original study, 'active smoking in subjects', was replaced by 'maternal smoking during pregnancy'. It was considered unlikely that active

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smoking would be a confounding variable in children under 5 years of age and none of the studies considered this variable. On the other hand, in utero effects of maternal active smoking could be a possible confounder relative to associations between postnatal maternal smoking and the respiratory system effects in infants that would otherwise be attributed to ETS exposure [1–3]. As can be seen from table 1, however, only 4 studies addressed this particular potential confounder. Item 22 ('others') was added when, in the course of this study, it became apparent that some confounders did not fit the 21 predetermined categories. As indicated in the body and footnotes of table 2, there were too few examples in this category (only 1 or 2 of each of the 5 different factors) to perform any valid analyses on their impact, if any.

Among the 21 potential confounders that we looked at, there was wide variation from study to study in their consideration. Only 7 of the 21 potential confounders (SES, family health history, subject's personal health history, family size, residence location, age and gender) were considered in 50% or more of the 41 studies. This is similar to what was found relative to the confounders considered in the majority of clinical endpoint studies of school-age or older children, i.e. SES, family size, residence location, age and gender. In both sets of clinical studies, the age of the subject and SES were the 2 most frequently considered confounders; addressed in 75–100% of the papers. The confounders that were considered relatively infrequently (in $<25\%$ of the studies) or not at all in the epidemiologic studies of pre-school children were other forms of indoor pollution, day care use, animal exposures, stress, dampness/cold, season, occupational exposures, nutritional status of the subject, and maternal smoking during pregnancy. Some of the very same confounders were considered infrequently in the studies of school-age or older children, namely, indoor pollution, day care use, animal exposures, stress, dampness/cold, season, occupational exposures and nutritional status [4].

Table 2 showed that there is wide variation from study to study in the array of confounders taken into consideration; a situation similar to that observed by us previously in studies of school-age children [4]. When evaluated on the basis of number of confounders considered per study (table 3), the representation in each paper is poor. Only 3 of the 41 preschool studies considered more than 10 of the 21 potential confounding variables, with the largest representation of confounders being 16 in 1 study. The situation was similar in studies of older children, where 7 of 45 papers considered 10 or more confounders, with the largest number of confounders considered being 12 [4].

The clinical endpoints were validated by medical records or physical examination in 21 of the 41 studies on preschool children, which is considerably greater than the 8 of 45 noted for studies in school-age children [4]. Nevertheless, it is noteworthy that in almost 50% of the studies, even in preschool children, clinical endpoints were not validated.

In the current report, 12 of the 21 potential confounders were analyzed in detail. Of those that have not been so analyzed, residence location, family size, outdoor pollution and quality of housing were considered in 23, 23, 16 and 9 studies, respectively. Of the remaining variables, animal exposures, stress, nutritional status and maternal smoking during pregnancy were considered in relatively few (1–4) of the papers, while occupational exposures, as in the case of school-age studies [4], were not considered at all.

Of the confounders examined in detail, a very large variety of specific criteria were used to define/determine SES, family health history, personal health history and age, in particular. This lack of standardization among these same potential confounding variables was also noted in our analysis of studies of parental/household smoking in school-age children [4, 5]

Table 12 summarizes our findings with regard to the issue of which confounders appear to be consistently associated with increased risk of respiratory illness in children. They are family health history, young age, male gender, personal health history and, although involving relatively few studies, day care use and season. Of these, family health history, male gender and personal health history were also found to be risk factors for respiratory illness, as well as influencing pulmonary function, in older children [4, 5].

As noted previously, family health history could influence the respiratory system through either genetic or infectious mechanisms [4]. Most of the available studies in preschool children observed no consistent association for SES, artificial feeding and gas fuel use/indoor pollution, or they were inconclusive (due to variable results or small numbers) relative to dampness/cold and heating/air-conditioning. These same factors were either not associated with endpoints or gave equivocal results in studies of school-age children [4].

In addition to a lack of standardization in the types of confounders considered, their specific criteria, the clinical endpoints examined and their validation, there was also marked variation in the statistical methodologies used to adjust for confounding variables in these epidemiologic studies of parental/household smoking in preschool chil-

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dren, as was commonly the case with studies in school-age or older children [4, 5].

As has been noted previously [4, 47], confounding variables may account for and/or contribute to effects that are associated with a presumed independent variable such as ETS, even in a dose-related fashion and even when associations between an endpoint and the confounder are not demonstrable. Furthermore, residual bias may persist even after adjustment of a confounder due to misclassification [47]. In addition to their individual influences, several potential confounders may interact with one another and this interaction may be inadequately addressed by standard methods [47].

Conclusion

While a perfectly designed epidemiologic study pertaining to the effects of parental/household smoking on respiratory illness and disease in preschool children may be difficult, if not impossible, to achieve, our analysis of the relevant studies in this area suggests the need for implementation of certain procedures in future studies. There is clearly a need for more consistent and comprehensive consideration of potential confounders. The potential confounders addressed should not only be those identified herein as having a strong influence on the respiratory system of preschool children but also those that appear to have little effect. For example, while a variable such as SES may have little influence on the incidence of respiratory symptoms and disease in children, it is also possible that the apparent lack of effect observed for SES could reflect the wide variation of criteria and lack of rigor used in its classification. Thus there appears to be a greater need to standardize as well as strengthen the criteria used for the identification of potential confounding variables in general. Furthermore, those potential confounders that have received relatively little attention to date (particularly those that intuitively appear to be important, such as indoor pollution, day care use, animal exposures, nutritional status and maternal smoking during pregnancy) should be considered in future studies. Further analysis should also take into consideration the potential influence of selected combinations of variables as well as their interactions. Finally, in addition to consistent validation of clinical endpoints (which is lacking to date), future studies should consider a standardization of experimental design, the questionnaire employed, the method of gathering information and statistical treatment of the data.

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